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Systematic review on effects of diet on gut microbiota in relation to metabolic syndromes

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Systematic review on effects of diet on gut microbiota in relation to metabolic syndromes

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Abstract

The microbiota is a complex ecosystem of microbes, the bulk of which reside mainly in the colon, and has been shown to be significantly influenced by the diet. The biological functions of the microbiota have been strongly linked to health and disease, including the development of metabolic syndrome (MetS). The aim of this paper was to review current literature on the effects of the diet on gut microbiota in relation to the development of MetS through the following objectives: (i) to determine how the diet influences the composition and functions of the microbiota; (ii) evaluate evidence of how this is linked with development obesity and biomarkers of MetS; (iii) investigate the significance of diet-microbiota interactions in relation to obesity and MetS. Multiple databases were used to find and collate relevant literatures. The main findings highlight that a plant-based diet, rich in indigestible carbohydrate was strongly associated with a richer, more diverse microbiota profile compared to a high-energy, high-fat Western diet. Studies in mice have indicated that weight gain can be induced via inoculation of an obese-type microbiota without changes in dietary intake. Additionally, polyphenols appear to interact with the microbiota, producing metabolites which have shown to possess more health potential than their precursors. Unabsorbed polyphenols also seem to beneficially modulate the microbiota, resulting in positive health outcomes. More *in vivo* human studies are necessary to conclude the significance of the

microbiota and mechanisms of action in the development of MetS. With this knowledge, there may be potential to manipulate the gut microbiota toward the generation of desired health outcomes as an alternative to pharmaceuticals.

Key words: microbiota, microbiome, metabolic syndrome, obesity, polyphenols, phytochemicals, dietary fibre

Abbreviations:

MetS – Metabolic syndrome; GI – Gastrointestinal; CHO – Carbohydrate; SCFAs – Short-chain fatty acids; AA – Amino acid; BCFAs – Branched-chain amino acids; TMAO – Trimethylamine-*N*-oxide; SFA – Saturated fatty acid; LPS – Lipopolysaccharide; LFHCC – Low-fat, high complex-carbohydrate; OM – Obesogenic microbiota; FMT – Faecal microbiota transplantation; GRP – G-protein-coupled receptor; PYY – Peptide YY; LGC – Low gene count; HBC – High gene count; GF – Germ-free; ANGPTL4 - Angiopoietin-like 4; LPL – Lipoprotein lipase; TJ – Tight junction

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1. Introduction

1.1 *Composition of the gut microbiota*

The Human Microbiome project has been one of the major influential projects in contributing to current understanding of the gut microbiota (Segata *et al.*, 2012). The microbiota is a highly complex ecosystem consisting of ~100 trillion diverse microbes, including yeasts, single-cell eukaryotes, viruses and parasitic worms (Bäckhed *et al.*, 2005), and is governed by age, diet, environment and the co-evolution of the gut microbes themselves (Ley *et al.*, 2008). The entire gastrointestinal (GI) tract is colonised with metabolically active microbes, but to varying degrees depending on the environment of the site; the colon harbouring the majority of bacteria found in the human body (Whitman *et al.*, 1998). Studies have demonstrated that two bacterial phyla dominate the gut microbiota – *Bacteroidetes* (Gram-negative), and *Firmicutes* (Gram-positive). While the human genome is comprised of approximately 22,000 protein-encoding genes, the microbiome equates over three million unique protein-encoding genes, which can change rapidly thus resulting in metabolic, transcriptomic and proteomic modifications. The main functions of the microbiota include fermentation of indigestible food components; vitamin and amino acid synthesis; production of short chain fatty acids; metabolism of dietary toxins and carcinogens; conversion of cholesterol and bile acids and maturation of the immune system (Li *et al.*, 2016). The relationship between the microbiota and human health appears to be bidirectional, rather than consequential, and there is also an environmental factor that affects the host metabolism and physiology. Current knowledge suggests that the composition and activity of the microbiota may influence early nutritional status, growth, energy balance, and individual susceptibility to infections and immune disorders throughout the lifespan (Agostoni & Kim, 2015).

1.2 Variation between individuals

At lower taxonomic levels, the mammalian microbiota is highly variable across individuals (Dethlefsen *et al.*, 2007). While it was once suggested that subjects could be grouped into one of three 'enterotypes', this has since been discredited, with well-supported evidence of continuous gradients present across individuals (Knights *et al.*, 2014). On one hand, genetics appear to have less of an impact on gut microbial composition than diet - even twins typically share no more than fifty percent of bacterial species (Turnbaugh *et al.*, 2010). On the other hand, the environment and close physical contact between individuals have shown to modify significantly the gut microbiota, with cohabiting family members sharing a similar composition (Song *et al.*, 2013). Healthy individuals are generally associated with a high level of microbial diversity and richness compared to individuals in sub-healthy condition such as obesity (Le Chatelier *et al.*, 2013, Cotillard *et al.*, 2013). Many studies have demonstrated that dysbiosis - disruption or imbalances in normal microbial composition - is associated with many major diseases (Petersen & Round, 2014), including obesity (Turnbaugh *et al.*, 2006) and diabetes (Qin *et al.*, 2012). It is assumed that higher levels of diversity within the gut helps better withstand stress and may help maintain stability due to competitive interactions (Coyte *et al.*, 2015). The composition of the gut microbiota is dynamic and intra-individual variability over time does exist, although to a lesser extent than inter-individual variation and on a species or strain-level (Costello *et al.*, 2009). However, individuals may possess different bacterial species that are responsible for catalysing the same reaction. Therefore, taxonomic variability of the gut microbiota is greater than functional variability (Turnbaugh *et al.*, 2009a). Microbial genes encoding a core activity will be present in every individual, forming a "functional core", while other activities may be restricted to certain individuals (Matthies *et al.*, 2009). The microbiota can be influenced by many external factors, but most significantly the diet. Dietary transition

through human history to the Western diet of today has resulted in substantial differences in the GI tract of humans though geographic differences have also been observed.

1.3 Dietary plant constituents in relation to obesity and MetS

Epidemiological studies have suggested a link between plant-based diets with reduced risk of diseases associated with metabolic syndromes (MetS), such as abdominal obesity, insulin resistance, hypertension and high cholesterol (Centritto *et al.*, 2009). Phytochemicals, defined as the non-nutritive, naturally occurring chemicals found in fruits, vegetables, wholegrains, legumes, beans, herbs, spices, nuts and seeds, are responsible for producing physiological properties as well as protecting against various environmental stressors of the plant crops. Polyphenols are a particularly widely studied group of phytochemicals, representing the largest and most widely distributed group of phytochemicals, with more than 8000 currently identified (Tsao, 2010). Recent research suggests that the interaction between polyphenols and gut microbiota may influence health and protect against the development of MetS.

Current strategies in control and management of the obesity epidemic focus on calorie-restriction, lifestyle modification and use of pharmaceutical agents. Weight loss drugs on the market are costly, often with side effects including cardiovascular complications or even suicidal tendencies (Baboota *et al.*, 2013). Antibiotics, while have demonstrated some benefits to microbiota modulation in relation to obesity, are not a realistic solution due to the impact on the normal microbiota and the potential for evolution of multi-drug resistant bacteria (Buffie & Pamer, 2013). Thus, the development of radical new treatments to curb the spread of chronic diseases across the world is essential.

2. Materials and methods

2.1 Data collection

Initial literature search commenced in October 2016. Literature from peer-reviewed journals and research papers were gathered from various databases such as Web of Science, Scopus and Medline. These databases were thought to be sufficient to fulfil the aims of this paper as they offer a broad range of current academic papers that are reliable and trustworthy, and allow efficient and specific searches to be carried out. Searches can also be refined or expanded by applying exclusion or inclusion criteria, assisting with finding papers that are most relevant to the project.

2.2 Eligibility criteria

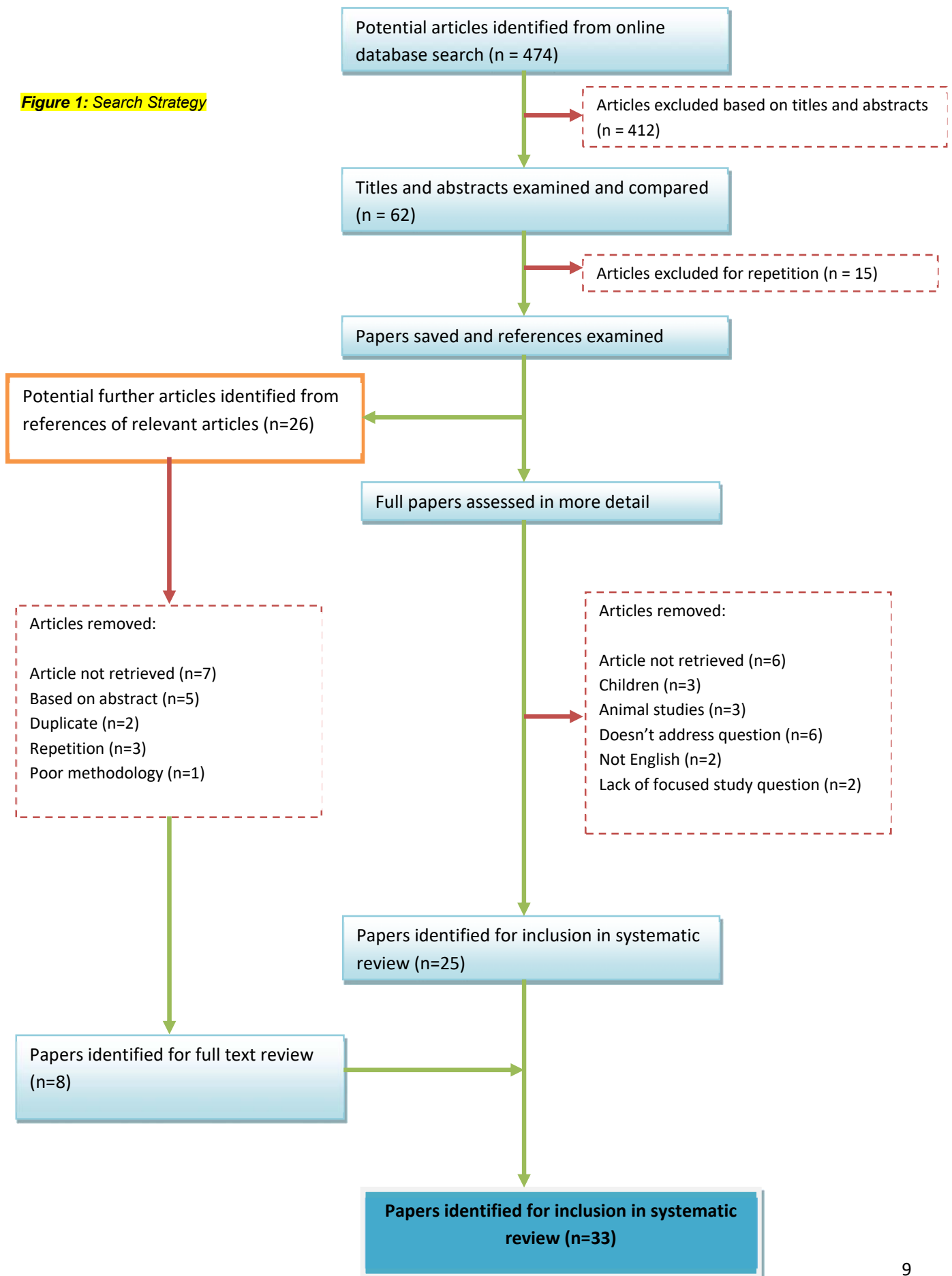
Papers were screened in order to efficiently identify the most relevant and appropriate papers. Exclusion criteria firstly included sources not written in English, as this may affect the ability to fully understand the content of the papers. Papers were also refined to those published from the year 2000 onwards, as this representing the largest scope of relevant up-to-date papers. Additionally, all papers were to relate to humans, excluding children, as this was deemed important for core papers in order to meet the aim. However, in some cases, *in vivo* animal studies were included where findings were deemed important. Final inclusion criteria included that full text must be available.

2.3 Search Strategy

Research commenced using keywords relevant to the topic, such as 'microbiota', and 'metabolic syndrome'. Each search was run through all three databases to ensure maximum coverage of relevant papers. The 'AND' function was utilised in order to refine and restrict searches, for example 'microbiota 'AND' 'metabolic syndrome' whilst the 'OR' function was also used to expand searches when necessary or to combine variations of a keyword that mean the same thing, for example 'microbiota' 'OR'

'microbiome'. Gaps in any information needed to fulfil the aims of the project resulted in further keyword searches, such as 'AND' 'health' OR 'nutrition'. When relevant, the truncation symbol (*) was utilised, so as all derivatives from that term were included in the search. For example 'gut micro*' searched for gut microbes, gut microbiota and gut microflora. This ensured as many relevant papers were identified as possible. Final searches included 'AND' 'metabolism' OR 'metabolic', as well as 'AND' 'energy absorption' OR 'nutrient absorption', but resulted in very few relevant papers. According to Hierarchy of Evidence, meta-analysis, systematic reviews and critically appraised articles were regarded as the highest quality types of studies respectively, followed by randomised-controlled trials (RCTs), cohort studies, case-controlled studies and reports, and finally, expert opinion. This was considered useful, as more time was spent analysing and reviewing those papers deemed more valuable as a priority, over those which may be less scientifically significant. It also allowed a better understanding of the strength of the evidence or information being analysed, enabling better quality and validity of results (*Figure 1*).

Figure 1: Search Strategy



3. Results

A total of thirty-three papers were included in the final core papers. The information within these papers was divided into four main codes (*Figure 2*) consisting of twenty-two codes (*Figure 3*). *Figure 4* depicts which types of paper were used in each theme.

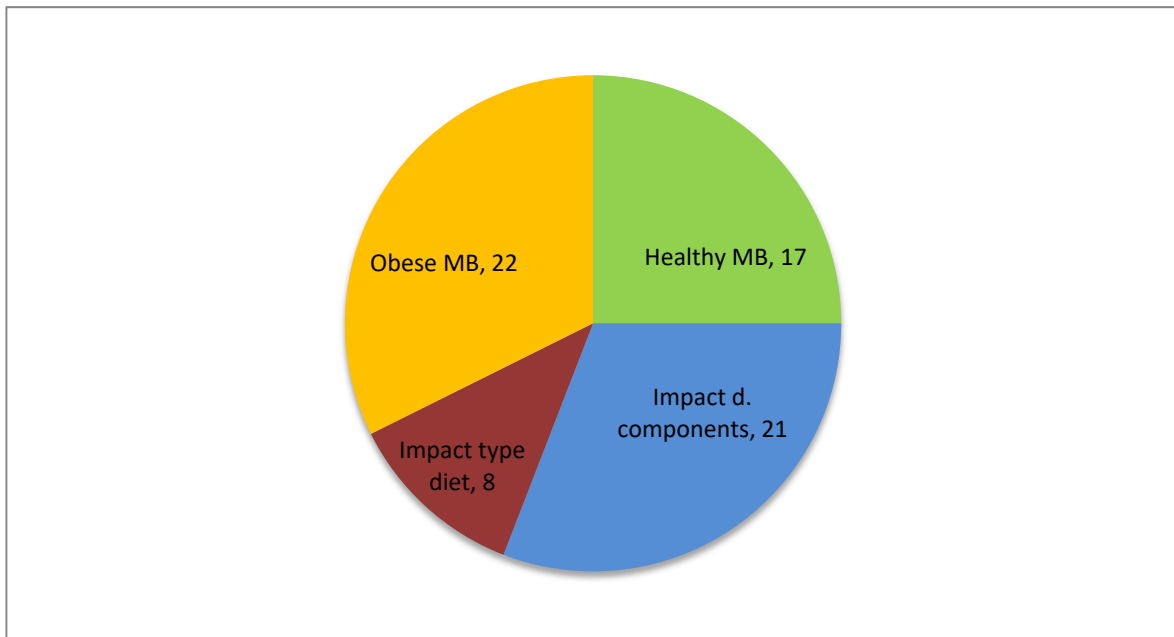
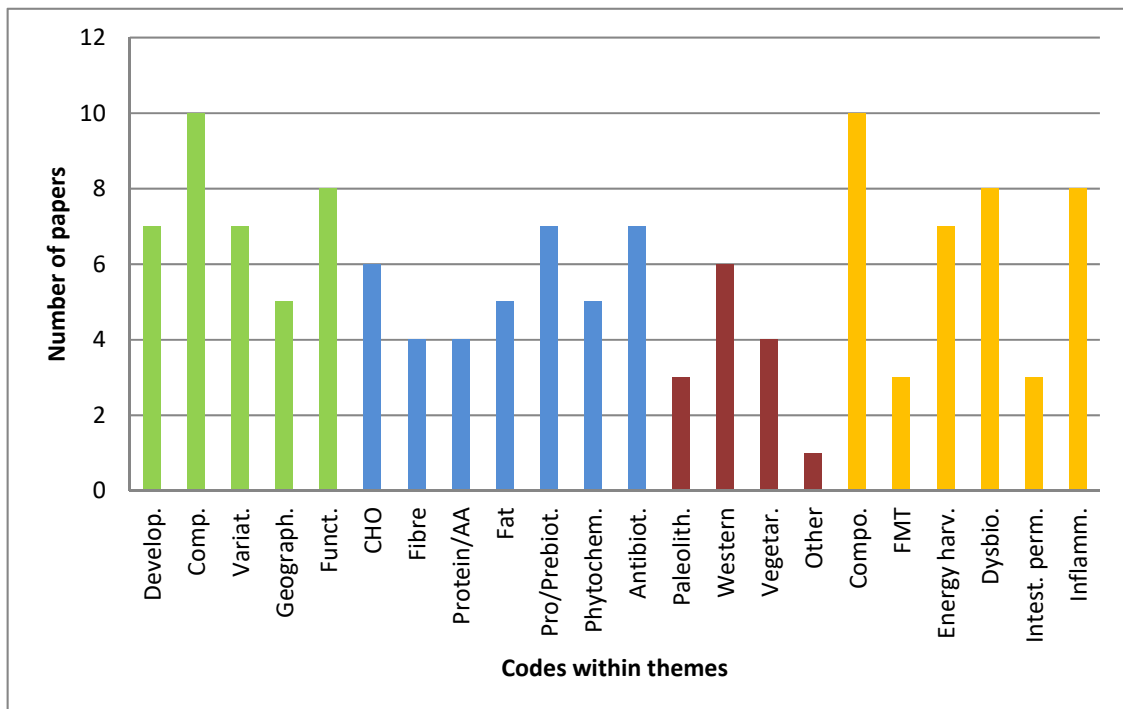


Figure 2: The number of core papers correlating to each theme. From the core papers chosen, the themes 'obese microbiota' and 'impact of dietary components' collated the most information, as each was a



key concept in over 50% of the total. The majority of information for the theme 'healthy microbiota' was collated from 17 core papers, and for 'impact of types of diet' was from 8 papers.

Figure 3: The number of core papers correlating to each individual code within each theme. Within the theme 'healthy microbiota', composition represented the largest code, with 10 corresponding papers. Within the theme 'impact of dietary components', probiotics and prebiotics and antibiotics were the most common however were deemed less relevant to the aim of this paper compared to carbohydrate and phytochemicals, which were the next largest code (6 and 5 papers respectively). The western diet was the most represented code within the theme 'impact of types of diet' (6 papers). 'Composition' was the largest code within the theme 'obese microbiota' (10), followed by dysbiosis and inflammation (8) and energy harvest (7).

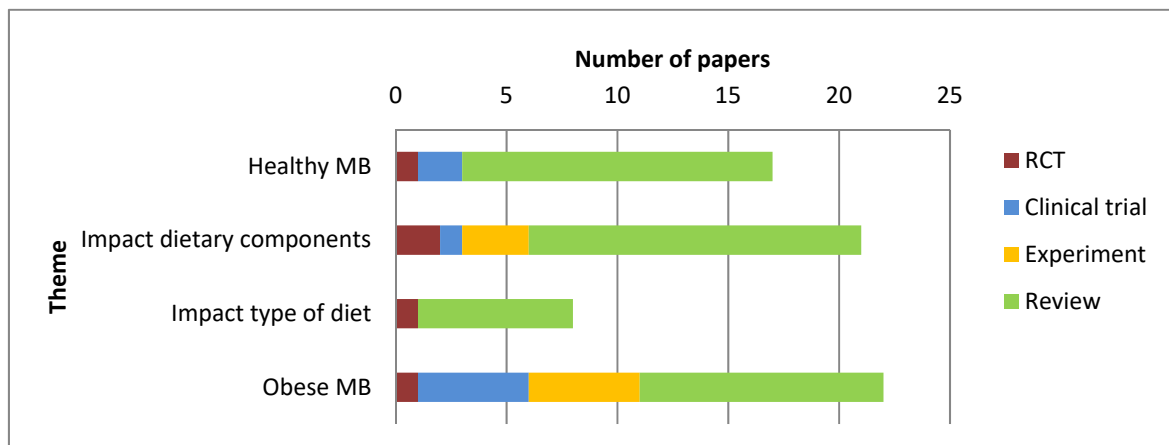


Figure 4: Number and type of core papers correlating to each theme. The results indicate that reviews were the most used source for each theme. Experiment studies were used for three themes, in particular, the 'obese microbiota'. Clinical trial core papers provided information for three of the identified themes. Randomised control trials were also used for all four themes, although typically they represented a smaller proportion of papers used for each theme.

4. Discussion

4.1 Establishment and development of the gut microbiota over the lifecycle

While unborn infants were previously thought to be sterile, the demonstration of microbes in the placenta, amniotic fluid and umbilical cord blood suggests a window of opportunity may lie prior to birth. Particular areas of enhanced colonisation are during

birth, feeding and weaning. Factors such as stress, a prolonged pregnancy and use of antibiotics may also affect intestinal colonisation within the infant. By the age of three, the infant microbiota resembles that of an adult. Extensive studies have shown that while intra-individual variability does exist, the overall gut microbiota is stable throughout adulthood. Sixty percent of the taxa found in the microbiota of an individual is still present after five years, suggesting the concept of a “core” microbiome (Faith *et al.*, 2013).

However, the elderly exhibit significant levels of inter-individual variation, possessing higher numbers of pathogenic bacteria and lower levels of probiotic microbes such as *Bifidobacterium*. Therefore, while the adult microbiota is relatively stable, studies suggest that old age significantly impacts on the composition of the gut microbiota. Lifestyle and nutritional aspects may also play a role, with differences being observed between elderly individuals in long-stay care and those in community-living (Claesson *et al.*, 2012).

4.2 Major functions of the microbiota

The host lives in symbiosis with their gut microbiota, but interactions range from mutualistic to parasitic. The microbiota performs many essential roles the human body otherwise cannot, and in its absence, nearly all aspects of host physiology are affected (Marchesi *et al.*, 2016). Thus, the microbiota can be regarded as a somewhat forgotten, yet critically essential organ.

The microbiota comes into contact with a wide variety of food components that escape upper gut digestion, namely complex indigestible carbohydrates (CHOs). Fermentation of indigestible CHOs and fibre is one of the main functions of the microbiota, while simultaneously providing the principle energy source for gut bacteria due to its enriched genes which are involved in CHO metabolism and uptake (Kurokawa *et al.*, 2007). The

utilisation of these dietary components may represent ten percent of daily energy intake (Fernandes *et al.*, 2014). Thus, the colon increases energy harvest from foods and plays a critical role in host metabolic functions (Tremaroli & Bäckhed, 2012), while influencing the bioavailability, synthesis and function of essential vitamins, minerals, macronutrients (He *et al.*, 2013). Fermentation of dietary polysaccharides produces acetate, propionate and butyrate, highly bioactive short-chain fatty acids (SCFAs), and gases such as carbon dioxide and hydrogen. These SCFAs act as an energy source for colorectal tissues, colonocytes and bacteria, as well as signalling molecules and modulating intestinal metabolism and inflammation (Fernandes *et al.*, 2014). Butyrate is regarded as beneficial for the host, promoting cell growth and acting as an anti-inflammatory (Hamer *et al.*, 2008). Acetate contributes to the synthesis of lipids and cholesterol within the body, while propionate can inhibit the function of acetate. Additionally, the microbiota also protects against opportunistic pathogens, directly preventing pathogens from attaching themselves to the host, as well as maintaining appropriate intestinal pH and outcompeting pathogens for nutrients. The microbiota also assures the establishment and maturation of the immune system and converts bile acids and cholesterol (Laparra & Sanz, 2010).

Conversely, the microbiota also possesses the ability to contribute towards chronic, metabolic and infectious diseases, as well as malnutrition. The microbiome and host genome differ, thus can either work in cooperation, or in conflict. Access to resources, such as food, may be foundation in shaping the interaction between microbiota and the host – for example – unlike fibre, simple carbohydrates can be used by both host and microbiome, thus competition arises over access to this nutrient, which can result in inflammation and adverse compositional changes in the microbiota (Wasielewski *et al.*, 2016).

4.3 Interaction between dietary components and the microbiota

4.3.1 Carbohydrate (CHO) and dietary fibre

CHO fermentation is the preferred energy source for the gut microbiota, which largely occurs in the proximal gut i.e. colon which contains the highest concentration of substrate availability (*Figure 5*). The amount of dietary CHO that comes into contact with the colon depends on many factors, such as meal size, chemical structure, food matrix and bolus, processing and preparation method (e.g. cooking), food form (e.g. whole food), rate of digestion and gut transit and the presence of enzyme inhibitors (e.g. tannins) (Cummings & Stephen, 2007). Foods that retain their structure throughout ingestion, such as wholegrains, protects CHOs from digestion in the small intestine, allowing a larger proportion to reach the colon. Here, they can be metabolised within the gut microbiota, providing an important source of CHO. The main CHOs for bacterial fermentation in the colon include indigestible CHOs such as polysaccharides, oligosaccharides and resistant starch and fibre.

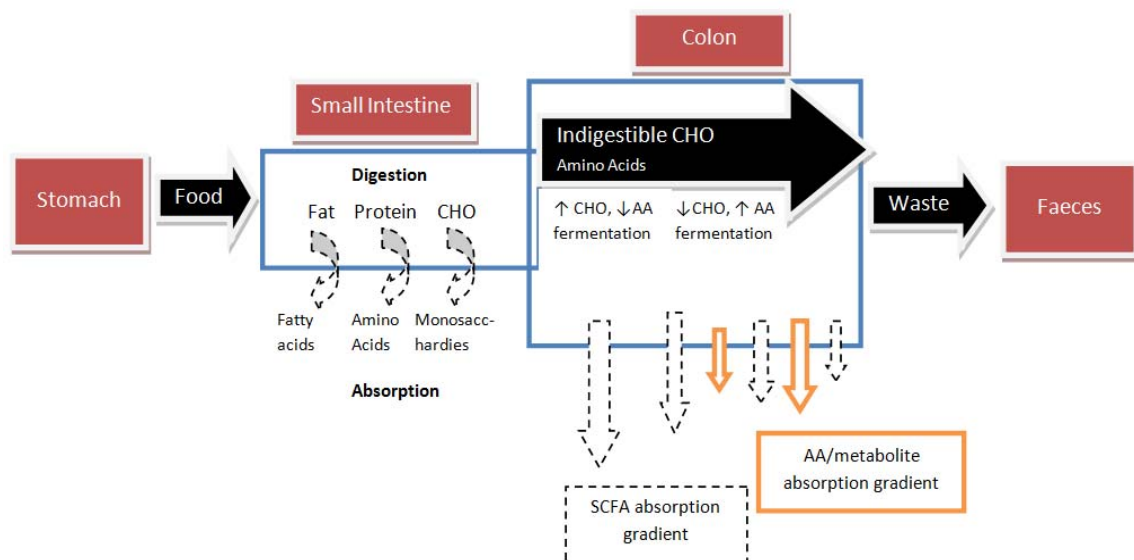


Figure 5: Progression of food through the gastrointestinal tract. Total SCFA concentration is highest in the proximal colon and decreases as the stool progresses along the colon due to their absorption. Due to this, along with progressive depletion of CHO substrates and increased protein fermentation, pH progressively increases from proximal to distal colon (Illustration created based on information of Windey *et al.*, 2011).

Certain bacterial species are associated with CHO consumption. For instance, a decrease in consumption of CHO in obese subjects results in a progressive reduction of *Bifidobacterium* (Hold *et al.*, 2003). Studies observing the impact of resistant starch on the microbiota composition have demonstrated that different type of resistant starch produces various results depending on the type of glycosidic linkage in the food and the functional capability of the gut microbes (Koropatkin *et al.*, 2012).

Foods rich in fibre are recognized to protect against overweight and obesity, and related diseases. There are clear epidemiological links between a diet high in fibre and improved MetS and reduced body weight, and a preventative and therapeutic effect of fibre on many disorders of the colon (Tuohy *et al.*, 2009). Subjects consuming a high fibre diet have shown to produce stools with a decreased pH compared to those on a low-fibre diet, which is associated with a higher production of SCFAs and subsequently, better regulation of intestinal bacterial community and reduced growth of pathogenic bacteria (Walker *et al.*, 2005).

4.3.2 Protein and amino acids (AAs)

Dietary protein provides colonic microbes with nitrogen for growth, absorption of CHO and production of SCFAs. It has been demonstrated that factors such as heat-processing, the food matrix, quantity ingested and the presence of compounds inhibiting proteolysis will influence the amount of dietary protein in the colon. While CHO fermentation is favourable, AA fermentation may occur in the event of CHO exhaustion either sourced from food or endogenous sources. There is substantially less

protein that reaches the colon compared to CHO, but as CHO is diminished during transit along the colon, AA fermentation begins to take over, resulting in a large range of metabolites and gases, such as amines, phenols, hydrogen sulphide, branched-chain fatty acids (BCFAs), ammonia and *N*-nitrous compounds, many of which are potentially cytotoxic, genotoxic or carcinogenic to human cells (Kovatcheva-Datchary *et al.*, 2009). Whether protein is beneficial or harmful for microbial health in the colon depends on the type of dietary protein and the interaction with other dietary components. For example, consumption of red meat is associated with higher concentrations of trimethylamine-*N*-oxide (TMAO), a microbial metabolite of L-carnitine, which may increase risk of atherosclerosis (Koeth *et al.*, 2013). High protein, low CHO diets have shown to result in decreased production of butyrate and *Bifidobacterium* levels compared with high CHO and fibre, low-fat diet (Brinkworth *et al.*, 2009).

Studies demonstrate that the amount of dietary protein consumed directly correlates with the amount of AA metabolites produced (Conlon & Bird, 2014), however, this is inconsistent across studies. Most ammonia for example, while potentially toxic, is excreted in the urine or faeces. Shoaie *et al.* (2015) demonstrated that obese individuals with low microbiome richness had elevated levels of certain AAs, such as phenylalanine and other branched-chain AAs, which are associated with T2D and insulin resistance. Diets promoting microbial protein synthesis that is associated with a richer microbiome, are better by means of converting AAs, excreting more nitrogen into the faecal stream, thus reducing plasma concentrations of nitrogen (Kramer *et al.*, 2012). This indicates other dietary constituents are also important in influencing how the microbiota responds to dietary protein.

4.3.3 Dietary fat & bile acids

The small intestine typically absorbs ninety-five percent of dietary lipids (Hinsberger & Sandhu, 2004). However, the rest often comes into contact with the colon. The effect of dietary fat on the gut microbiota is thought to be largely influenced by bile acids. Bile acids are steroids found within bile and conjugated with glycine by the enzyme cholesterol 7 α -hydroxylase in the liver to form bile salts. Primary bile acids are synthesised in the liver (De Aguiar-Vallim *et al.*, 2013), while secondary bile acids are produced by gut microbes from primary bile acids by 7 α -dehydroxylation (Ou *et al.*, 2012). A high animal-fat diet has shown to increase the amount of bile acids which escape the SI and enter the colon and are subsequently available for microbial metabolism. The presence of bile acids in the colon seems to exert strong selective pressure, with only microbes being able to withstand bile acid conditions and to survive, thus restricting the growth of many microbes (Kurdi *et al.*, 2006). Secondary bile acids are pro-inflammatory and may be carcinogenic and involved in the development of disease of the GI tract. However, they can also inhibit colonisation of certain pathogens, such as *Clostridium difficile* (Buffie *et al.*, 2015). Therefore, the regulation of hydrolysis of primary bile acids into secondary bile acids needs to be further understood.

Importantly, the type of fat may have vastly different effects on the microbiota. It is accepted that unsaturated fat can benefit circulatory health, and studies have also demonstrated that it may protect against weight gain (Caesar *et al.*, 2015). This is an unsurprising finding which may highlight the effects of fat on microbial metabolic activity and subsequently on host health, however, this needs to be further investigated. Conversely, saturated fatty acids (SFAs) have the ability to provide membrane substrates for pathogens such as *E. coli*, subsequently reducing bacterial energy requirements, promoting its survival (Yao & Rock, 2015).

High-fat diets and those high in emulsifiers, for example in processed food, may also thin the mucus barrier, which protects the epithelium from colonisation and invasion from pathogens, this contributing to a less favourable composition in the microbiota (Wasielewski *et al.*, 2016).

4.4 Impact of different diets on the microbiota

Evidence that rapid dynamic changes (over 24-48 hours) can take place in the microbiota in response to dietary changes. Gut microbes are extensively purged every one to two days and have the ability to double in number within the space of an hour. This is demonstrated by several dietary intervention studies, which produce reproducible and significant shifts the microbiota that can overcome interpersonal variation in extreme cases. However, the shifts in response to daily variation in the diet are at the genus and species level, rather than at the phylum level. Additionally, the subject's microbiota tends to revert back to the state prior to the intervention, suggesting that long-term diet is the primary driver in determining one's gut microbiota (Xu & Knight, 2015).

4.4.1 Palaeolithic diets and an evolutionary mismatch

The rapid simplification of the diet since industrialisation has occurred at a much faster rate than the human genome can possibly adapt. Bengmark (2013) reports that the human microbiome is not dissimilar in fact to our palaeolithic forefathers living 200,000 years ago, despite a vastly different diet. This adaptive lag is hypothesised to be central to many of today's diseases, such as heart disease and obesity (Eaton *et al.*, 2002). It is argued by many that it is unlikely that neither the human genome, nor the microbiome, will ever adapt to the Western diet (Carrera-Bastos *et al.*, 2011), and that

humans will always be genetically programmed to consume a diet much more similar to that of Paleolithic times, rather than the modern diet.

4.4.2 Western diets

Low microbial genomic richness is generally observed in those consuming a Western diet, which is a potential contributing factor to associated disorders, such as MetS (Le Chatelier *et al.*, 2013). This sub-optimal microbiota is likely due to a depletion of metabolic fuels, and can lead to dysbiosis, malfunction and increased plasma endotoxin levels. Subjects consuming a Western diet demonstrated a seventy-one percent increase in concentrations of endotoxin in plasma (endotoxemia) compared to controls (Pendyala *et al.*, 2012), suggesting a disruption of intestinal barriers and increase in Gram-negative bacteria in the microbiota (Haro *et al.*, 2016). These are in turn associated with inflammation and risk of development of chronic disease (Bengmark, 2013). A high-energy diet, whether from fat or CHO, in mice has shown to result in increased levels of lipopolysaccharides (LPS), which are the components of endotoxins and gram-negative bacteria, and may be responsible for certain biological activity such as inducing inflammation. A high-fat diet has also been found to produce a stronger response compared to high-CHO (Pussinen *et al.*, 2011). These indicate that overconsumption of energy can disrupt intestinal barriers, causing inflammation, and counteract the otherwise beneficial effects seen with consumption of indigestible CHO.

One study switched humanised mice from a low-fat, high-CHO, plant-based diet to a typical Western diet high in fat and sugar and observed a reduction in Bacteroidetes (Turnbaugh *et al.*, 2009b). The principle findings of a study conducted by Haro *et al.* (2016) in twenty obese adult men were an increased abundance of *Prevotella* and decrease in *Roseburia* following consumption of a low-fat, high complex-carbohydrate

(LFHCC) diet, compared to an increase in *Roseburia* and *Oscillopsira* following administration of a Mediterranean style diet. Correlation analysis between individual diet-induced changes in bacterial genera and species and individual diet-induced changes in metabolites showed that the changes in seven metabolites in faeces and three metabolites in plasma were related to the changes in three bacterial genera and two bacterial species. It is projected that the increase in *Prevotella* in the LFHCC may enhance ability to harvest energy from resistant starch and oligosaccharides and other CHOs that escape SI digestion. These studies suggest that compositional changes occur within the microbiota due to diet, which can result in metabolic shifts, with more energy extracted from food and therefore available for the host. However, this finding appears to run in contrast to the work indicating LFHCC diets lead to a more beneficial microbiota, thus complicating these findings. The LFHCC subjects also showed elevated butyrate-producing *F.prausnitzii*, which is negatively associated with T2D inflammatory biomarkers (Furet *et al.*, 2010). The anti-inflammatory effect may in part explain why the LFHCC diet does not necessarily lead to increased weight gain despite increased energy harvest.

4.4.3 Vegetarianism and veganism

Herbivores show enriched concentrations of enzymes involved in biosynthesis of AAs and a more diverse microbial community compared to carnivores, who show higher numbers of enzymes responsible for branched-chain AA degradation (Muegge *et al.*, 2011). In human participants, it has been observed that fat and protein from animal sources, compared to a high-CHO plant-based diet, decreased microbial diversity and richness (Wu *et al.*, 2011). Many human studies, however, remain inconclusive in this area, with conflicting results reported. For example, where one study reported high concentrations of several *Clostridium* clusters associated with strict vegetarians, another reported lower proportions of *Clostridium* in vegetarians compared to meat-

eaters (Zimmer *et al.*, 2012). More large-scale studies under more similar conditions may improve the consistency of findings.

Subjects consuming a vegan or vegetarian diet have displayed a lower stool pH compared to controls, limiting growth of *E. coli* in the gut. As previously discussed, red meat intake is also associated with increased concentration of plasma TMAO, which is dependent of specific gut microbes and linked to an increase of *Prevotella*. The microbiota of vegetarians and vegans, in contrast, are poor producers of TMA, which is required for oxidation into TMAO, even when precursor compounds are temporarily incorporated into the diet (Koeth *et al.*, 2013). Diets higher in animal proteins also tend to increase sulphur compounds in the microbiota, compared to plant-based diets which are higher in methane; however, the significance of this is not yet quantified (Magee *et al.*, 2000). Contrasting results in human studies have also been observed in terms of microbial diversity between vegetarians and omnivores, some reporting that vegetarians have increased diversity and no difference being observed in others; however, it is usually agreed compositional changes certainly exist. The changes in microbiota composition may, therefore, play a role in the beneficial health effects associated with a more plant-based diet and lower intake of animal products.

4.4.4 Other diets

Interestingly, a gluten-free diet in healthy subjects showed a reduction in microbial communities generally regarded as beneficial for the host, such as *Bifidobacterium* and *Lactobacillus*, with an increase in *E. coli* and other opportunistic pathogens (De Palma *et al.*, 2009). This may be explained by a lower intake of polysaccharides as an energy source and prebiotic for beneficial bacteria. This hypothesis has been tested by administration of a gluten-free, but high polysaccharide diet (Sanz, 2010).

The genome of the gut microbe *Bacteroides plebeius* in Japanese communities, where consumption on uncooked seaweed is common, has shown to retain β -porphyrase, an enzyme capable of digesting algal cell walls (Hehemann *et al.*, 2010). This is not observed in most other communities. The evidence, therefore, supports the hypothesis that to a certain extent, the composition and functions of the microbiota co-evolves with the host and can adapt to specific macronutrients and to suit the requirements of the host depending on dietary intake. Personalised response to foods is imperative in understanding why it is unlikely that one diet or dietary component will tailor to all needs, or affect all populations in the same manner (Zeevi *et al.*, 2015).

Therefore, it is evident from current knowledge that dietary components consumed and the type of diet as a whole have the capacity to positively or negatively impact the compositional profile of the microbiota, potentially contributing towards the development of MetS. However, these must be investigated further to consolidate current findings and to assess their relevance to the current incidence of MetS. The findings seem coherent with current knowledge on dietary factors known to be associated with the development of, or protection against, MetS. The interplay of the microbiota, therefore, may be yet another layer of complexity to the story which should be considered when regarding MetS aetiology.

4.5 The association between the microbiota, obesity and MetS

While the main cause of obesity is an excessive energy intake, the wide variation between individuals in microbiota composition and energy-harvest abilities may highlight the complexity of the development and treatment of obesity and associated diseases. Potential associations between the gut microbiota and obesity relate to energy balance, glucose metabolism and low-grade inflammation.

4.5.1 Features of the obese-type microbiota

The commensal bacteria within the microbiota appears to be of importance in weight gain and fat storage. Differences in the relative abundance of Bacteroidetes and Firmicutes in obese and lean individuals seem to be the most commonly reported. Studies have demonstrated that there was an enhanced abundance of Firmicutes and reduced Bacteroidetes abundance in the microbiota of obese mice (Ley *et al.*, 2005). This association was later observed in obese human subjects during a dietary intervention study. Furthermore, there appeared to be an increase in Bacteroidetes following weight loss (Ley *et al.*, 2006). This ratio of Firmicutes and Bacteroidetes is also observed in T2D patients (Larsen *et al.*, 2010). However, this association remains controversial, with other studies reporting the opposite effect or no significant changes (Collado *et al.*, 2008; Duncan *et al.*, 2008). Lower taxonomic changes have also been observed, and this may be a more accurate dysbiosis associated with obesity, however, as of yet, findings are complex and may be within the species-, rather than genera-level (Million *et al.*, 2012).

The obesogenic microbiota (OM) is believed to be inflammatory and show lower levels of bacterial richness and diversity. Pathways for the production of SCFAs are elevated in obese and overweight subjects, thus increasing the amount of fermentable substrates and calories available for the host. The OM also appears to have a lower potential for butyrate production and induce weight gain via modifying gene expression involved in absorption of dietary CHO and fat (Bäckhed *et al.*, 2004).

The OM has displayed an enhanced capacity for energy harvest from the diet, a feature which appears to be transmissible as demonstrated by faecal microbiota transplantation (FMT) studies. SCFAs also act as signalling molecules which influence energy intake and metabolism, binding to G-protein-coupled receptors (GRP) 41 and 43 (Conterno *et al.*, 2011). Activation of GRP41 and GRP43 by SCFAs induces the release of 5-

hydroxytryptamine (5-HT) and peptide YY (PYY), increasing colonic mobility and efficiency of energy harvest (Samuel *et al.*, 2008). The release of PYY in the plasma induces feelings of satiety (Delzenne *et al.*, 2011). Thus, production of SCFAs may reduce appetite and help regulate food intake.

4.5.2 *Significance of microbiota richness and diversity*

Shoaie *et al* (2015) observed that obese individuals with low gene count (LGC) within the microbiome demonstrated an impaired metabolic phenotype compared to subjects with high gene count (HGC), such as poor glucose homeostasis and insulin resistance. HGC subjects also produced higher levels of SCFAs important for metabolism and providing energy for beneficial microbes and colonocytes. Other studies have demonstrated that obese individuals with LGC showed improvements in gene richness following diet-induced weight loss associated with improved metabolism, highlighting the significance of a HGC and diversity in metabolic health (Sonnenburg & Bäckhed, 2016; Cotillard *et al.*, 2013).

4.5.3 *Studies in germ-free mice and faecal microbiota transplant*

The discovery that conventional mice store forty-two percent more body fat and forty-seven percent more gonadal fat than germ-free (GF) mice, despite lower food intake, sparked the beginning of investigations on the microbiota as a potential factor influencing obesity. Subsequent studies have demonstrated that colonisation of GF mice with gut microbiota from conventional mice resulted in a sixty percent increase in body fat and increased levels of insulin resistance, adipocyte hypertrophy and circulating leptin and glucose. Partly, this is due to the ability of the microbiota to ferment indigestible polysaccharides, which can be absorbed as monosaccharides and increase hepatic lipogenesis. In addition, colonisation of a gut microbiota in GF mice suppresses intestinal expression of angiopoietin-like 4 (ANGPTL4), an inhibitor of

lipoprotein lipase (LPL) and subsequently, this leads to increased uptake of fatty acids (Bäckhed *et al.*, 2004). Others have repeated similar studies, inoculating GF mice with the microbiota of either obese mice or obese humans, resulting in weight gain and increased accumulation of fat without changing dietary pattern or energy intake (Cox *et al.*, 2014) quite possible due to an enhanced capacity for energy harvest from the diet. In fact, GF mice seem to be protected against diet-induced obesity even when fed a high-fat, high-sugar diet (Bäckhed *et al.*, 2007), with better insulin sensitivity and glucose tolerance compared to conventional mice fed the same diet (Rabot *et al.*, 2010). Transplant of the microbiota of lean subjects into subjects with MetS via FMT showed to improve insulin sensitivity and increase microbiota diversity and abundance of *Roseburia intestinalis*, subsequently increasing butyrate concentrations in stools (Vrieze *et al.*, 2012). Studies have demonstrated that lean phenotypes are also transmissible via inoculation, reversing weight gain induced by introduction of an OM into GF mice (Ridaura *et al.*, 2013). Therefore, this may be some of the most convincing evidence of a causal relationship between gut microbiota and excessive weight gain, or at least that the microbiota certainly plays a role. However, results following inoculation with a lean phenotype were diminished if fed a diet high in saturated fat and low in fruit and vegetables, highlighting that although microbiota composition is a reflection of the individual, the importance of the diet on its function.

4.5.4 Low-grade inflammation and intestinal permeability

Obesity and the development of MetS are associated with low-grade inflammation, which has been linked to excess circulating LPS. LPS is produced continually in the colon via degradation of gram-negative bacteria. As previously discussed, endotoxemia is associated with a Western diet, and continuous low-rate infusion of LPS has also been linked with excessive weight gain, hyperglycaemia and insulin resistance in mice

studies (Harte *et al.*, 2010; Creely *et al.*, 2007). In addition, mice injected with LPS showed an increase in weight and insulin resistance. In contrast, mice lacking LPS receptors were shown to be protected against MetS following infusion of LPS or administration of a high-fat diet, suggesting a causal link to LPS and LPS-receptors with obesity and MetS. Furthermore, *Bifidobacterium*, often shown to be reduced in obese subjects, has shown to be negatively correlated with concentration LPS and endotoxemia (Cani *et al.*, 2007), which could, therefore, be another explanation for increased levels of inflammation observed in obese individuals. Evidence has shown that intestinal barrier function is largely controlled by tight junctions (TJs), and is important for protecting against pathogens and food antigens (Menard *et al.*, 2010).

4.6 Effect of dietary plant constituents on the microbiota

4.6.1 Bioavailability and their metabolites in the microbiota

A wide variety of functional components within plant species have been suggested to effect on microorganisms either directly or indirectly (Gyawali and Ibrahim, 2021). Previous work on polyphenols, one of the major dietary plant constituents, focused on the effect of native compounds, which demonstrated poor absorption and bioavailability and rapid elimination from the body. However, biological functions still existed, raising doubt as to the relevance of these studies. Growing evidence suggests that their metabolites may be more biologically active and proposed health effects may therefore be based on their bioavailability and metabolites produced (Delmas *et al.*, 2011). As humans cannot effectively digest plant cell walls, this may be a mechanism by which phytochemicals can make it to the gut microbiota. Only ten per cent of polyphenols are absorbed within the SI into the blood (Clifford, 2004), while the ninety percent of non-digested phenolics that reach the colon undergo extensive transformation by specific components within the gut microbiota (Scalbert *et al.*, 2002). The evidence that

metabolites are produced by microbial action has been shown in several studies, demonstrating a lower bioconversion in subjects administered antibiotics prior to flavonoid consumption and from the lack of polyphenol metabolites detected in germ-free rats (Possemiers *et al.*, 2011).

4.6.2 Effects of polyphenols on microbiota function and composition

Unabsorbed dietary polyphenols and their metabolites have shown abilities to modulate the gut microbiota, exerting stress or stimulus effects. The main benefit of polyphenols in modulating the microbiota is thought to be due to their antimicrobial effect. Phenolic compounds derived from tea have demonstrated inhibitory effects on both the growth and adhesion of pathogenic bacteria, such as *Clostridium spp.*, *E. coli* and *Salmonella typhimurium*, while promoting proliferation and adhesion of beneficial bacteria, such as *Lactobacillus* or *Bifidobacterium* (Gyawali & Ibrahim 2012; Lee *et al.*, 2006). Thus, the antimicrobial effect of polyphenols appears superior to that of antibiotics, which reduce beneficial, as well as harmful bacteria. Such selective bactericide effect has also been demonstrated across several studies with different phenolic compounds (Krogus-Kurikka *et al.*, 2009). For example, oxalic acid and phytic acid appear to bind to iron, thus microorganisms requiring iron for growth, such as pathogens, are outcompeted by microorganisms not requiring iron for growth (Gyawali & Ibrahim, 2012). Polyphenols were found to be able to reduce concentrations of pathogenic bacteria while increasing beneficial microbe populations. Therefore, polyphenols appear to modulate the composition of the microbiota towards a more beneficial profile, which would subsequently benefit host health.

Phenolics have been proposed as a novel therapeutic strategy in the prevention of obesity and MetS via microbial modulation and prevention of dysbiosis in the microbiota. Quercetin and resveratrol treatments have shown to reduce fat

accumulation and weight gain in some studies, but not others (Mosele *et al.*, 2015).

Further studies in this area are necessary to pinpoint other mechanisms of action of polyphenol metabolites in relation to the development of MetS. A brief overview of the main interactions between the microbiota and polyphenols is depicted in *Figure 6*.

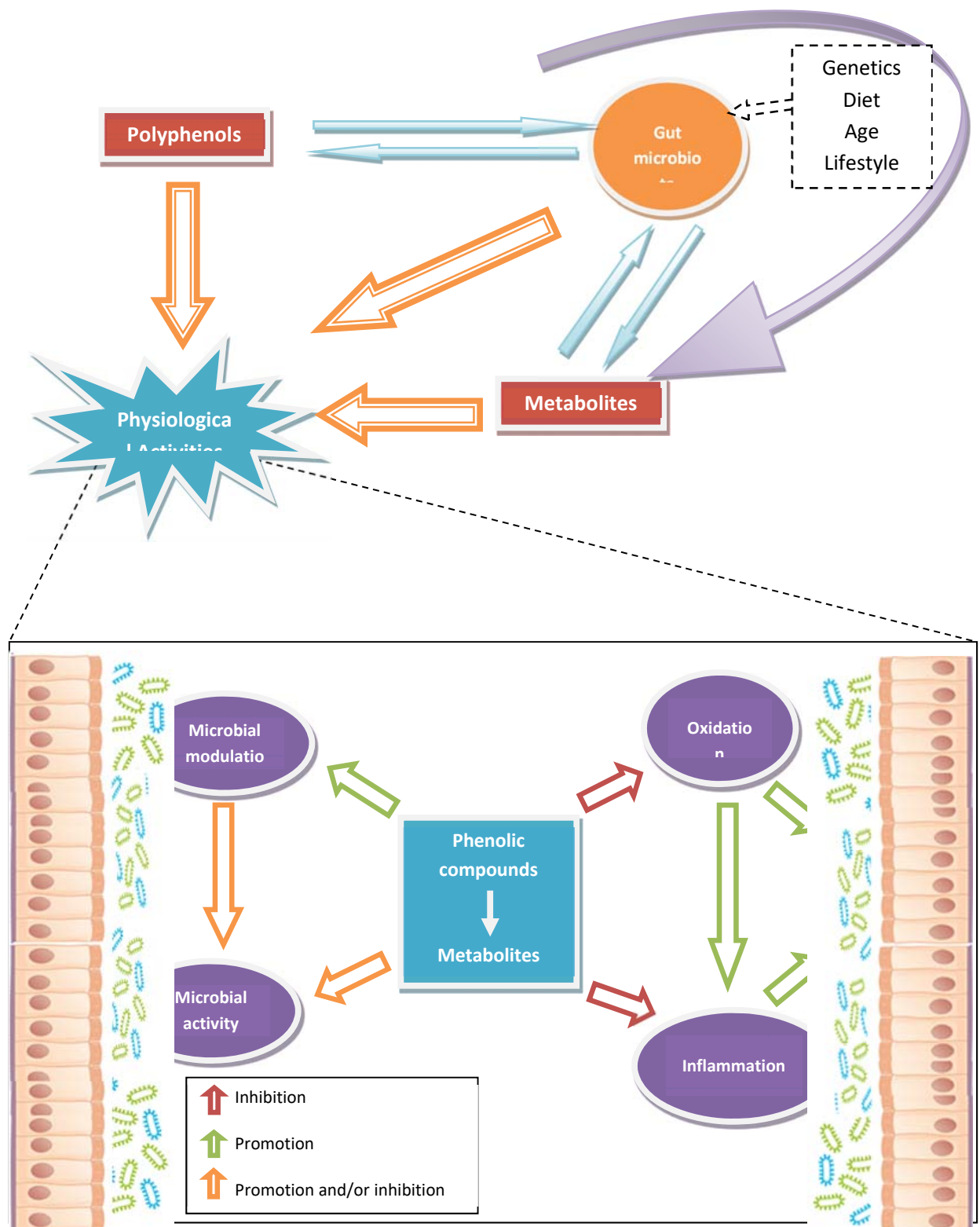


Figure 6: Diagram to show a summary of the main interactions between the microbiota and polyphenols

5. Conclusion

While understanding of the microbiota has advanced significantly, many studies show contrasting results or are inconclusive and with this being further complicated by the heterogeneity observed across individuals and the complexity and variation in the diet. However, it appears that a plant-based diet rich in indigestible CHO is associated with a healthy microbiota profile, while the Western diet, excessive in energy, high in fat and red meat, and low in fruit, vegetables and dietary fibre, is associated with dysbiosis and a less favourable gut microbiota. Most studies are consistent in suggesting that an obese-type microbiota is enriched in Firmicutes and reduced in Bacteroidetes, with a lower overall abundance and diversity and enhanced capacity for energy harvest and inflammation.

Research has demonstrated that the polyphenol metabolites produced by the gut microbiota are more biologically active than their precursors. Unabsorbed polyphenols have shown to exert specific antimicrobial effects within the microbiota, inhibiting the growth of pathogens without affecting, or even stimulating, the growth of commensal bacteria, thus beneficially modulating the gut microbiota. Therefore, the microbiota seems to positively respond to dietary polyphenols, although changes appear to be at class-, family-, genus- and species-level rather than at phylum-level. It is likely that many positive effects exerted by polyphenols are not due to just one group, but of multiple biological activities from a range of metabolites.

6. Future Perspectives

More *in vivo* human studies are necessary to better understand the significance of this complex ecosystem in the development of MetS. With this knowledge, there is the potential to manipulate the gut microbiota to generate desired shifts in microbial populations and health outcomes.

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